## REMARKS/ARGUMENTS

Claims 1 and 2 are presently pending and under examination.

Claims 1 and 2 have been amended above to define Applicants invention with greater particularity. The amendment to claim 1 is supported throughout the specification, for example, at page 22, lines 17-22. Claim 1 has merely been amended to rearrange the phrase "functional fragment." Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants have set forth above the amendment to claims 1 and 2 in clean form above and in Appendix A, with marked up amendments indicated with brackets and underlining.

### Rejections under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description respectfully is traversed.

The current Office Action repeatedly refers to *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), going as far as to claim at page 6, that it is the "seminal case" on written description and basing the present rejection for lack of written description on largely on the *Lilly* decision. Applicants respectfully direct

the Examiner's attention to the more recent Federal Circuit decisions that have explicitly distinguished the *Lilly* decision.

In the recent decision of *Moba v. Diamond Automation*, 325 F.3d 1306, 66 USPQ2d 1429 (Fed.Cir. 2003) the Federal Circuit stated:

> [C]ase law reflects two applications of [the written description requirement,] . . . "[t]he function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him. . . . In that setting, the written description is the metric against which a subsequently added claim is measured to determine if it is due the priority date of the original patent. . . . The second application of the written description requirement is reflected in Regents of the *University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997). There, this court invoked the written description requirement in a case without priority issues, [requiring a] precise definition of a DNA sequence in the patent specification. **In more recent cases, however, this court has distinguished *Lilly*. . . . The *Lilly* disclosure rule does not require a particular form of disclosure** because one of skill could determine from the specification that the inventor possessed the invention at the time of filing.

*Id.* at 1319 (Emphasis added).

Similarly, in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002), the Federal Circuit indicated that neither the specification nor the deposited biological material recited the precise "structure, formula, chemical name, or physical properties" required by *Lilly*. *Id.* at 1324 (quoting *Lilly*, 119 F.3d at 1566). Although the Federal Circuit had initially determined that the specification in *Enzo* did not satisfy the *Lilly* disclosure rule, it revisited the issue and remanded to the district court, instructing the court below as follows:

> On remand the court should determine whether a person of skill in the art would glean from the written description, including information obtainable from the deposits of the claimed sequences, subsequences, mutated variants and mixtures sufficient to demonstrate possession of the generic scope of the claims.

*Enzo*, 296 F.3d at 1328.

Similarly, in its first pronouncement following *Enzo*, the Federal Circuit again noted:

> More recently, in *Enzo Biochem*, we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, **the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.**

*Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1332, 65 USPQ2d 1385, 1399 (Fed. Cir. 2003)(Emphasis added).

Finally, citing again from the Federal Circuit's most recent pronouncement, the concurring opinion in *Moba* by Judge Rader states:

> The language of § 112, ¶ 1 indicates that a patent will contain an adequate description if it provides enough information to enable a person skilled in the art to make and use the invention. Any disclosure that enables one to make and use the invention also, by definition, also shows that the inventor was in possession of that full invention. Consequently, **the erroneous written description requirement of *Lilly* case lacks both a statutory and a logical foundation.**

*Moba* at 306 F.3d at 1323 (Emphasis added).

> **Fortunately, the viability of the *Lilly* rule is on the decline.** After *Enzo*, this court recognized "that *Ely Lilly* did not hold that all functional descriptions of genetic material necessarily fails as a matter of law -- to meet the written description requirement, rather, **the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure."**

*Id.* at 1326 (Emphasis added).

Claim 1 is directed to a butyrylcholinesterase variant encompassing substantially the same amino acid sequence shown as SEQ ID NO: 2, or a functional fragment thereof, wherein said variant or functional fragment thereof has a Tryptophane at amino acid position 328. Claim 2 is directed to the butyrylcholinesterase variant of claim 1, having a 15-fold increase in cocaine hydrolysis activity.

The specification teaches at page 22, lines 17-28, that the invention provides a butyrylcholinesterase variant shown as SEQ ID NO: 2 that has substantially the same amino acid sequence as human butyrylcholinesterase, but includes at amino acid position 328 of human butyrylcholinesterase (SEQ ID NO: 17) a Tryptophane (W) substitution in place of the encoded Alanine (A) residue. In the same paragraph, the specification also teaches that the A328W butyrylcholinesterase variant (SEQ ID NO: 2) was obtained by PCR site-directed mutagenesis of human butyrylcholinesterase as described in Example I and exhibits at least a fifteen-fold increase in cocaine hydrolysis activity compared to human butyrylcholinesterase. Applicants respectfully submit that, to a person with knowledge of the art the disclosed function of at least a fifteen-fold increase in cocaine hydrolysis activity compared to human butyrylcholinesterase is sufficiently correlated to a particular, known structure, in particular the change at amino acid position 328 of human butyrylcholinesterase (SEQ ID NO: 17), where a Tryptophane (W) takes the place of the encoded Alanine (A) residue.

Generally, with regard to the variants of the invention, the specification, at page 8, lines 5-8, teaches that a variant molecule has substantially the same amino acid sequence as butyrylcholinesterase and exhibits cocaine hydrolysis activity, for example, reduced, substantially the same or increased cocaine hydrolysis activity compared to butyrylcholinesterase. The specification further teaches that a variant can have at least 70% identity to the reference butyrylcholinesterase and can have a single amino acid alteration as well as multiple amino acid alterations compared to buyrylcholinesterase.

The specification further provides written description of substantially similar sequences, which are described as polypeptides, fragments or segments that have an identical amino acid sequence, or a similar, non-identical sequence that is considered by those skilled in the art to be a functionally equivalent amino acid sequence and is at least 70% identical in sequence to the reference butyrylcholinesterase. The specification provides further description of substantially similar amino acid sequences by describibg that such sequences include polypeptides encompassing, for example, modified forms of naturally occurring amino acids such as D-stereoisomers, non-naturally occurring amino acids, amino acid analogues and mimetics so long as such polypeptides retain functional activity, in particular, cocaine hydrolysis activity. With regard to modified amino acids and their uses, which are well known in the art, the specification teaches that such modifications can be useful to optimize functional activity, stability or

bioavailability, and provides citations to two texts routinely consulted by those in the art that provide further guidance with regard to amino acid modification (specification, page 27, lines 18-29).

Applicants respectfully submit that the written description provided by the specification regarding the variants and substantially similar sequences demonstrates not only that Applicants contemplated the invention, but also shows that Applicants were in possession of the claimed invention at the time of filing. The disclosed function of at least a fifteen-fold increase in cocaine hydrolysis activity compared to human butyrylcholinesterase is sufficiently correlated to a particular, known structure, in particular the change at amino acid position 328 of human butyrylcholinesterase (SEQ ID NO: 17), where a Tryptophane (W) takes the place of the encoded Alanine (A) residue. Accordingly, Applicants respectfully request removal of the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description.

Rejections under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, respectfully is traversed.

The recitations of "butyrylcholinesterase variant" and "substantially the same" allegedly render the claims indefinite because each of the terms is allegedly relative (current Office Action mailed February 4, 2003, Paper No. 15, paragraph bridging pages 3 and 4). Applicants respectfully submit that each of the terms is clear and definite when viewed in its proper context.

A seminal case on the construction of the second paragraph of § 112 is *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970), where the CCPA observed:

> The first sentence of the second paragraph of § 112 is essentially a requirement for precision and definiteness of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends that claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

*Id.* at 909, 164 U.S.P.Q. at 645-46 (footnote omitted).

The Federal Circuit has since had the opportunity to decide a number of § 112, second paragraph issues. It is clear from these decisions that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *See, e.g., In re Marosi*, 710

F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983); *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 U.S.P.Q. 1 (Fed. Cir. 1984); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983); and *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 U.S.P.Q.2d 1225 (Fed. Cir. 1999) (district court failed to consider the knowledge of one skilled in the art when interpreting the patent disclosure).

> The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, e.g., competitors of the patent owner, can determine whether or not they infringe. That determination requires a construction of the claims according to the familiar canons of claim construction.

*All Dental Prodx, LLC v. Advantage Dental Prods.*, 309 F.3d 774, 779-80, 64 USPQ2d 1945, 1949 (Fed. Cir. 2002) (citations omitted). One of those canons is that claims are construed as one skilled in the art would understand them in light of the specification of which they are a part. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1575, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). Indeed, a patentee may be his or her own lexicographer by defining the claim terms. Another one of those canons is that a patentee need not define his invention with mathematical precision in order to comply with the definiteness requirement. *In re Marosi, supra*, at 802-03.

For the reasons that follow, Applicants submit that the claims, including the phrases "butyrylcholinesterase variant" and "substantially the same" are written in such a way to give notice to the public of the subject matter claimed.

With regard to the variants of the invention, the Office asserts that although the specification sets forth that a variant can have at least 70% or more sequence identity, the claims are not so limited (current Office Action mailed February 4, 2003, Paper No. 15, paragraph bridging pages 3 and 4). Applicants respectfully submit that the specification , at page 8, lines 5-8, defines the term variant as referring to a molecule that has substantially the same amino acid sequence as butyrylcholinesterase and exhibits cocaine hydrolysis activity. The specification further teaches that a an amino acid that is substantially the same can have at least 70% identity to the reference butyrylcholinesterase. Therefore, while the Office asserts that the claims are not so limited, Applicants submit that they are entitled to define the claim terms and, further, that the claims are to be read and interpreted in light of the specification according to the controlling federal court decisions cited above.

The phrase "substantially the same" is similarly clear and definite to the skilled person. In this regard, the specification teaches starting at page 9, line 20, that when used in reference to an amino acid sequence, the phrase is intended to mean a polypeptide, fragment or segment having an identical amino acid sequence, or a polypeptide, fragment or segment having a

similar, non-identical sequence that is considered by those skilled in the art to be a functionally equivalent amino acid sequence. An amino acid sequence that is substantially identical to a reference butyrylcholinesterase or butyrylcholinesterase variant of the invention is further defined as having at least 70%, at least 80%, at least 81%, at least 83%, at least 85%, at least 90%, at least 95% or more identity to the reference butyrylcholinesterase. Substantially the same amino acid sequence is further taught to include polypeptides encompassing, for example, modified forms of naturally occurring amino acids such as D-stereoisomers, non-naturally occurring amino acids, amino acid analogues and mimetics so long as such polypeptides retain functional activity.

In view of the above, Applicants respectfully submit that claims 1 and 2 are clear and definite when viewed in their proper context. Accordingly, Applicants request removal of the rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

## Rejections under 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 1 and 2 under 35 U.S.C. § 102 subsections (a), (b) and (e), as allegedly anticipated by Broomfield et al., U.S. Patent No. 6,001,625, respectfully is traversed. Applicants further traverse the rejection of claims 1 and 2 also stand rejected

under 35 U.S.C. § 102 subsections (a) and (b), as allegedly anticipated by Sevigny et al., WO 99/66072.

The Examiner alleges that this patent discloses variants that differ by only one amino acid from presently claimed SEQ ID NO: 2 and, accordingly, are "substantially the same" so as to anticipate claim 1. As amended herein, base claim 1 recites that the variant or substantially similar sequence thereof has the amino acid Tryptophane at position 328. Neither of the cited references disclose a butyrylcholinesterase that has the amino acid Tryptophane at position 328.

Therefore, since the cited references not disclose all elements of claims 1 and 2, the present rejections under 35 U.S.C. § 102 subsections (a), (b) and (e), as allegedly anticipated by Broomfield et al., U.S. Patent No. 6,001,625, and, separately, under subsections (a) and (b), as allegedly anticipated by Sevigny et al., WO 99/66072, are unsupported by the cited references and should be removed.

Non-Statutory Double Patenting

Applicants respectfully traverse the rejection of claims 1 and 2 as allegedly unpatentable for non-statutory double patenting over claim 10 of U.S. Patent No. 6,001,625. The Examiner asserts that the claims, although not identical, are not patentably distinct.

Claim 10 of U.S. Patent No. 6,001,625 neither teaches nor suggests a butyrylcholinesterase variant or substantially similar sequence thereof that has the amino acid Tryptophane at position 328. Accordingly, Applicants respectfully request that the rejection of claims 1 and 2 as allegedly unpatentable for non-statutory double patenting over claim 10 of U.S. Patent No. 6,001,625, is unsupported by the cited patent and should be removed.

## CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned attorney with any questions related to this application.

Respectfully submitted,

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